Double-Blind Controlled Clinical Trial of Clofazimine in Reactive Phases of Lepromatous Leprosy*

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Summary: A double-blind controlled trial in 24 lepromatous leprosy patients in reaction showed that clofazimine (Lamprene) controlled symptoms of erythema nodosum leprosum reaction in lepromatous leprosy better than prednisolone. Clofazimine also appeared to be significantly superior in preventing recurrence once the reaction had been controlled. There was a statistically significant rise in serum albumin among inpatients on clofazimine as compared with patients on prednisolone, but no difference in terms of neurological status, bacterial index, morphological index, and renal functions. Red/black hyperpigmentation was seen among practically all patients on clofazimine. No other side-effects or deleterious systemic effects were observed.

Introduction

Lepromatous leprosy patients present a wide clinical spectrum, complicated further by their tendency to develop "reactions" while on treatment. These reactions vary in severity from acute brief episodes to recurrent and chronic exacerbations. While mild reactions are easily controlled with simple drugs, such as aspirin, chloroquine, parenteral antimony, and indomethacin, patients with severe erythema nodosum leprosum syndrome who are very ill and toxic respond only to large doses of corticosteroid (Jopling, 1964; Karat *et al.*, 1970). Such doses produce serious complications and have no antibacterial effect. Therefore search for an effective antileprosy drug which can suppress episodes of reaction continues.

Clofazimine (Lamprene; G30.320; B.663), a riminophenazine derivative, is reported to have an anti-inflammatory effect (Browne, 1965; Hastings and Trautman, 1968; Imkamp, 1968) in addition to specific activity against the leprosy bacillus (Browne and Hogerzeil, 1962a, 1962b; Williams *et al.*, 1965; Pettit and Rees, 1966; Pettit *et al.*, 1967). It is also effective in suppressing further exacerbations (*British Medical Journal*, 1969).

Double-blind controlled clinical trials were set up at the Schieffelin Leprosy Research Sanatorium, Karigiri, to evaluate objectively the efficacy of clofazimine in the various phases of lepromatous leprosy in comparison with conventional therapy. One such trial dealt with lepromatous leprosy patients who were admitted with severe reactions and had not responded to conventional anti-inflammatory therapy. The objectives of this trial were to evaluate the efficacy of clofazimine at the dosage level of 100 mg. three times a day in (*a*) reducing the severity of reaction and eliminating all symptoms of erythema nodosum leprosum, (*b*) improving the neurological and haematological status, (*c*) improving liver and renal functions, (*d*) reducing bacterial and morphological indices, (*e*) eliminating side-effects if any, and (*f*) preventing further reactions. In this preliminary communication observations made on 24 patients are reported.

Material and Methods

Clofazimine 100 mg. three times a day for 12 weeks was compared with prednisolone given according to the following schedule: 10 mg. thrice a day for the first week, 10 mg. twice a day for the second week, 5 mg. thrice a day for the third week, 5 mg. twice a day for the fourth week, and 5 mg. once a day for the subsequent eight weeks.

Patients who had a history of three or more severe reactions and whose current reaction was 3+ or 4+ (see Table I), which could not be controlled by antimony, aspirin, or chloroquine, were included in this series. Patients who were known to have radiologically proved peptic ulcer, those with intercurrent acute infections, and those with tuberculosis or malignant lesions were excluded from the trial. Patients satisfying the criteria for inclusion were assigned to clofazimine or to prednisolone according to the list of random allocations prepared earlier and kept confidential at the pharmacy.

TABLE I.—*Grading of Reactional Status*

Grade	Symptoms and Signs					Oral Temperature	
	Erythema Nodosum Leprosum	Subcutaneous Nodules	Periosteitis, Neuritis, and Arthritis	Oedema	Others	°F	°C
1+	Few. Superficial. Not tender	Nil	Pain but not tenderness	±Minimal	—	99–101	37·2–38·3
2+	Scattered. Mostly superficial. Slightly tender	±	Some tenderness	±Moderate	—	99–103	37·2–39·4
3+	Multiple, superficial and deep. Painful and tender	±	Painful and tender	±Gross	±Iritis. ±Tender and painful lymphadenitis	99–105	37·2–40·6
4+	Multiple, superficial and deep. Very painful and tender. Necrotic	±	Very painful and tender	±Gross	Iritis. Very painful and tender lymphadenitis. Toxic state with distress	99–105	37·2–40·6

Packages of these two drugs labelled serially 1, 2, 3, etc., were given to patients as they entered into the trial.

The past history, the present complaints, the findings at detailed physical examination, and the results of laboratory investigation of each patient were recorded on a special form.

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At monthly intervals thereafter the findings of physical examination and laboratory investigations were noted on a separate form to indicate progress.

Treatment was regarded as successful when at the end of 12 weeks the reaction was controlled, as judged by the maintenance of body temperature at less than 99°F., (37.2°C.) no new erythema nodosum leprosum lesions, no pain in the peripheral nerve, no progression of neurological deficit, and iritis quiescent in two weeks from starting treatment. Treatment was regarded as having failed when the reaction was not controlled, as indicated by a temperature of over 100°F. (37.8°C.) for three weeks, recurrent crops of new erythema nodosum leprosum lesions, progressive clinical deterioration of the patient's general condition as evidenced by persistent tachycardia, progressive fall in blood pressure, "toxic state," and progressive weight loss while on trial. Patients who developed tuberculosis and other major intercurrent infection, persistent symptoms of peptic ulcer, or gastrointestinal bleeding were removed from the trial.

Twelve patients in each of the two drug groups were observed for more than four months. These groups were similar in terms of sex, age distribution, and duration of leprosy. There was no difference in past history of reactions (number and severity) and severity of erythema nodosum leprosum lesions at entry into the trial (Table II).

TABLE II.—*Reactional Status of Patients under Trial in the Two Drug Groups*

Case No.	Past History of Reaction: Duration (Months)	Past History of Reaction: Total No. of Reactions	Past History of Reaction: Reaction Rate per 12 Months	Grade of Current Reaction
		Clofazimine		
1	15	5	4	4+
3	19	7	4·4	4+
5	28	11	4·7	4+
8	4	4	12	4+
12	48	18	4·5	4+
15	25	10	4·8	4+
16	12	4	4	4+
19	36	8	2·7	4+
20	24	20	10	4+
23	10	5	6	3+
24	20	8	4·8	3+
25	17	10	7·0	3+
		Prednisolone		
2	30	6	2·4	4+
4	40	21	6·3	4+
7	10	6	7·2	4+
10	17	8	5·6	4+
11	36	11	3·7	3+
13	28	8	3·4	3+
14	99	27	3·3	4+
17	6	5	10	4+
18	23	11	5·7	3+
21	18	4	2·7	4+
22	150	16	1·3	4+
26	9	5	6·7	4+

Results

Control of the reaction as judged by criteria given earlier is shown in Table III. The reaction was controlled in 11 of the 12 patients on clofazimine but in only 3 of the 12 on prednisolone. This difference is highly significant ($P < 0.001$). The clinical condition of five patients on prednisolone greatly deteriorated, with recurrent/chronic erythema nodosum leprosum, high fever, and toxic state, necessitating removal from the trial, but for none of those on clofazimine was removal necessary.

TABLE III.—*Control of Reaction*

Control of Reaction	Clofazimine: No.	Clofazimine: %	Prednisolone: No.	Prednisolone: %
Yes	11	91·7	3	25·0
No	1	8·3	9	75·0
Total	12	100·0	12	100·0

Recurrence of reactions among patients whose initial reaction was controlled is given in Table IV. It is interesting that after the initial control of reaction, clofazimine suppressed further episodes in all but one case. The number in whom initial control of erythema nodosum leprosum was obtained in the prednisolone group is too small for any definite conclusions to be drawn regarding suppression of recurrence.

TABLE IV.—*Recurrence of Reactions During Trial*

Reactions	No. of patients: Clofazimine	No. of patients: Prednisolone
Nil	10	2
Grade 2	1	—
Grade 3	—	1
Total	11	3

In none of the patients under trial was there any deterioration of neurological function as judged by sensory testing with No. 5 nylon, manual muscle tests, and electrical tests with "strength-duration" curves. The morphological indices of patients in both groups were zero or near zero at the beginning of the trial. There was no appreciable change during the trial. The bacterial index (0 to 6, Ridley's scale) did not show any appreciable change in either group. This was to be expected as the trial was for only 12 weeks.

During the trial there was no appreciable change in body weight in both groups. The blood pressure remained normal throughout. While most cases showed an increase of at least 10% from the initial value in haemoglobin and packed cell volume, the difference between the two drug groups was not statistically significant. Significantly more patients on clofazimine than on prednisolone showed reduction of leucocyte count of more than 10% of the initially raised value. Similar declines were seen in the neutrophil count. Though the erythrocyte sedimentation rate (E.S.R. Westergren) remained high most patients in both groups showed some decline. The difference in the two drug groups regarding changes in total protein was not significant, but a greater number of patients on clofazimine showed a rise in serum albumin. The decrease in globulin was not appreciably different in the two drug groups.

The side-effects observed in the groups are shown in Table V. The most obvious seems to be red/black pigmentation in patients on clofazimine. Five of the patients on prednisolone developed "puffiness" of the face. Termination of trial because of side-effects was not necessary in any patient.

TABLE V.—*Side-effects Observed During the Trial*

Side-effects	Clofazimine: No.	Clofazimine: %	Prednisolone: No.	Prednisolone: %
Red/Black pigmentation	12	100·0	—	—
Hyperpigmentation	—	—	1	8·3
Puffiness of face	—	—	5	41·7
No side-effect	—	—	6	50·0
Total	12	100·0	12	100·0

Comments

The effect of anti-inflammatory therapy varied from complete subsidence in minor grades of reaction to partial remission in the severer cases. The progressive deterioration in the clinical status of some patients in chronic reaction could not be controlled and resulted in their death. Even drugs such as prednisolone at 30 mg. have not been consistently success-

ful, especially in controlling severe grades of reaction. The patients in this trial were all 3+ or 4+ grade of reaction at entry and had a history of similar reactions for months or years. In the random allocation, since both the groups consisted of patients with a similar severe reactional status, the comparative findings may be considered valid even though the trial was brief; for clofazimine in a dosage of 300 mg. a day dramatically controlled severe reactions as compared with prednisolone in the dosage used.

Considerably higher doses of prednisolone might have controlled the acute phase of the reaction. In such patients, however, it would be necessary to maintain the prednisolone at levels greater than 30 mg. a day for weeks to keep the reaction under adequate control. Such treatment in our experience led to severe complications in most cases, usually reactivation of tuberculosis, osteoporosis, fracture, and perforation of peptic ulcer.

In none of the patients on clofazimine was it necessary to discontinue treatment owing to deterioration, while in five patients on prednisolone it did become necessary. In the dosage used clofazimine was well tolerated and did not have any significant side-effect except hyperpigmentation. None of the patients was unhappy about this phenomenon; they were pleased to exchange pigmentation for chronic invalidism.

These patients must be observed for a longer period before comment can be made on the prophylactic efficacy of clofazimine in suppressing recurrence of reaction, but during this trial the number showing recurrence was small. The duration of the trial was also not long enough to assess the effect of clofazimine on lepra bacilli. This is under investigation in a double-blind trial in patients with untreated lepromatous leprosy.

The present study shows that clofazimine in a dose of 100 mg. three times a day is an effective treatment for severe erythema nodosum leprosum reaction in lepromatous leprosy and that it improves liver function in these chronically debilitated patients as judged by an appreciable rise in serum albumin levels. We were unable to find any deleterious effects of clofazimine on the cardiovascular, respiratory, alimentary, genitourinary, and nervous systems under the conditions of the trial at a dose of 300 mg. a day as judged by clinical and laboratory assessments.

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Place of Culdocentesis in the Diagnosis of Ectopic Pregnancy

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Summary: In developing countries the high incidence of anaemia and pelvic infection often makes the diagnosis of ectopic pregnancy difficult. Culdocentesis has been used in 100 doubtful cases out of 144 consecutive cases of ectopic pregnancy. The preoperative diagnosis was correct in 93 out of the 100 cases. There were three false-negative and four false-positive results; only two unnecessary laparotomies were performed. It is suggested that culdocentesis has an essential place in the early diagnosis of doubtful or atypical ectopic pregnancy. It was simple, safe, and reliable. Owing to earlier diagnosis maternal mortality and morbidity and the duration of stay in hospital have all been reduced.

Introduction

Ectopic pregnancy is common in the tropics. Lawson and Stewart (1967) reported this as the commonest surgical emergency occurring in the West Indies. The diagnosis of ectopic pregnancy may be the most perplexing in gynaecology. In developing countries the high incidence of anaemia and pelvic infection greatly adds to the difficulty in diagnosis. Even if catastrophe is avoided, delay in making the diagnosis increases the chances of significant morbidity and incapacity of the patient (Riva *et al.*, 1962). Continued observation in doubtful cases may lead to prolonged hospital stay, which a developing country or any other can ill afford with the present shortage of hospital beds generally.

The occasional report advocating culdocentesis has appeared in the American literature. Many British gynaecologists are still of the opinion that the procedure is of limited value and may be misleading and dangerous (Douglas, 1963). The present study was undertaken to investigate the place of culdocentesis in the early diagnosis of ectopic pregnancy.

Materials and Methods

All cases of ectopic pregnancy admitted to the department of obstetrics and gynaecology between January 1966 and February 1969 were included in this study. In this period there were 22,912 live births and stillbirths and 144 ectopic

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